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Effect of Intravenous Ibuprofen on Ischemia-Reperfusion Injury Following Perioperative Tourniquet in Patients Undergoing Total Knee Arthroplasty

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Abstract

Oxidative stress occurs in the organism with ischemia due to tourniquet use and subsequent reperfusion. Oxidative stress increases postoperative morbidity. Some Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) perform their anti-inflammatory effects in part by binding or inhibiting their formation of active oxygen radicals at the site of inflammation. In this study, we aimed to evaluate the effect of IV ibuprofen on ischemia-reperfusion injury (IRI) in patients undergoing total knee arthroplasty over oxidative stress parameters. The patients were randomly divided into two groups. Each patient's protocol number, age, sex, body mass index (BMI), additional disease, drug use, tourniquet time, hemoglobin value, additional analgesic requirement and application, adverse reaction development on the first postoperative day were recorded in the research follow-up form. Both groups of patients; before anesthesia, 45 minutes after tourniquet application, 5 minutes after tourniquet lowering, 20 minutes after tourniquet lowering and at 24th-hour post-op; TOS, TAS, paraoxonase, arylesterase, myeloperoxidase, catalase, ceruloplasmin, albumin, IMA, thiol-disulfide balance tests were studied. Statistical analysis of test results was performed. We observed that antioxidants decreased and oxidants increased on the first postoperative day in both groups in patients who underwent total knee arthroplasty. The decrease in antioxidant parameters was higher in IV ibuprofen doses compared to the control group in the case group; these doses indicate that the drug adversely affects the organism in the fight against oxidative stress, which is an undesirable effect. To evaluate this negative effect of IV ibuprofen which is increasingly

used in postoperative analgesia, studies with different doses of drugs and different surgeries may be needed.

Keywords

Ischemia-Reperfusion, IV Ibuprofen, Oxidative Stress, Knee Arthroplasty, Non-Steroidal Anti-Inflammatory Drugs

1. Introduction

Inflammatory response and oxidative stress are the most important factors in surgical trauma [1]. This is even more important in orthopedic surgeries that develop ischemia-reperfusion injury (IRI). Therefore, it was thought that reducing the inflammatory response and oxidative stress will positively affect post-op morbidity [2]. Pneumatic tourniquets are frequently used in orthopedic surgery to reduce blood loss and provide a clear surgical field. Arterial blood pressure increases during the tourniquet, hypoxia, acidosis, and hyperkalemia occur in ischemic areas. When the tourniquet is lowered, metabolites in the ischemic area enter the systemic circulation and initiate hypotension and hypoxia. Free oxygen radicals are produced in abundance with reperfusion and oxygenation, leukocyte activation and endothelial damage occur. Free oxygen radicals cause peroxidation of polyunsaturated fatty acids in membrane and plasma proteins and can inhibit major mitochondrial respiratory chain enzymes and cause major organ dysfunction [3]. Intravenous (IV) ibuprofen is a drug with anti-inflammatory, analgesic, antipyretic properties [4]. Some Non-Steroid Anti-Inflammatory Drugs (NSAIDs) perform their anti-inflammatory effects in part by binding or inhibiting the formation of active oxygen radicals in the inflammation zone [1]. There is no literature on this effect of IV ibuprofen. In this study, we aimed to evaluate the effect of IV ibuprofen on ischemia-reperfusion injury in total knee arthroplasty over oxidative stress parameters.

2. Materials and Methods

After obtaining the approval of the ethics committee, this research was presented and approved to Yıldırım Beyazıt University Projects Office as a Scientific Research Project (BAP). In addition to the general anesthesia consent form, the informed consent form was obtained for the study and included in the study. Patients who were planned to undergo regional anesthesia were excluded from the study. The patients included in the study were between 50 - 75 years of age, ASA physical status I-III and body mass index (BMI) were 23 - 40. Excluded criteria was a history of allergy to ibuprofen or other NSAIDs, gastric or duodenal ulcer, gastrointestinal bleeding, chronic kidney disease, hemodialysis, liver dysfunction, history of uncontrolled hypertension, myocardial ischemia, dementia, stroke or other CNS disease, severe psychiatric disease, Patients with alcohol or

drug abuse, suspected malignant hyperthermia in his or her family history, and expectation of difficult intubation. Patients were randomly divided into two groups. Each patient's name-surname, protocol number, age, gender, BMI, additional disease, drug use, tourniquet time, hemoglobin value, additional analgesic requirement and administration, and post-op first-day adverse reaction development were recorded in the research follow-up form. Vital signs (SpO_2, pulse, mean arterial pressure) of the patient before anesthesia, 45 minutes after inflating tourniquet, 5 minutes after tourniquet lowering, 20 minutes after tourniquet lowering, and post-op 24th-hour were recorded in the study follow-up form. The patients included in the study were randomly divided into two groups. The group to be given IV ibuprofen (case group) was named as "Group V" and the control group as "Group K". Case group patients received 800 mg + 400 mg + 400 mg of medication for a total of 1600 mg in 24 hours. Although the maximum daily dose of IV ibuprofen is 3200 mg, it is due to information on the geriatric population in the prospectus which is "Due to possible side effects, caution should be exercised during use in elderly patients. In general, treatment should be started with the lowest dose, liver, kidney and heart functions of the patient should be monitored and there should be no concomitant disease or other medication. Elderly patients have an increased risk of serious gastrointestinal adverse events." Half of the maximum daily dose was used. Preoperative sedation medication was not administered to the patients before entering the operation room. It was ensured that the patients to be included in the study did not take antioxidant drugs and did not smoke in the last 24 hours. In both patient groups, 20 G catheters were placed into the antecubital vein and blood samples were taken before being taken to the operation room. The vial containing 800 mg/8ml ibuprofen IV infusion ((INTRAFEN Gen Pharmaceuticals and Health Products Industry and Trade Ltd. Co.) to Group V was then infused intravenously in 30 minutes by diluting the solution with 500 ml 0.9% NaCl (before the tourniquet was inflated).

Group K was infused for 30 minutes without IV medication with a 500 ml 0.9% NaCl solution. After these procedures, the IV catheter was washed with saline to collect only blood. Patients were admitted to the operation room in the supine position, were placed on the operating table and were subjected to standard monitoring (Electrocardiography, peripheral oxygen saturation, non-invasive blood pressure). 2.5 mg/kg propofol to both groups from another vascular route at induction (Propofol 1% Fresenius Kabi), 0.6 mg/kg rocuronium (Esmeron 5 mg, 5 ml vial, Organon) 1 mcg/kg remifentanil (Ultiva, GlaxoSmithKline) were administered and the patient was intubated endotracheally. Standard maintenance was performed with sevoflurane, 1 MAC, 2 lt/min oxygen, 2 lt/min air, and 0.125 mcg/kg/min remifentanil infusion. The mechanical ventilator was adjusted to maintain end-tidal partial carbon dioxide pressure ($EtCO_2$) between 30 - 35 mmHg for respiratory control. To reduce the effect of surgical stress on the gastrointestinal system, 50 mg/2ml ranitidine was administered intravenously in 1

minute in both groups. Pneumatic tourniquet (VBM Medizintecnik GmbH Tourniquet 5800 and/or ELC) pressure was applied to be 2 times the systolic artery pressure. In cases where the automatic tourniquet was preferred, Ringo brand tourniquet was determined according to the body of the patients and applied to the patient after surgical field disinfection. Tourniquet time was recorded in both groups. 45 minutes after tourniquet application (ischemia), TOS in both groups (Total Oxidant Status, Rel Assay Diagnostics), TAS (Total Antioxidant Status, Rel Assay Diagnostics), paraoxonase (Rel Assay Diagnostics), arylesterase (Rel Assay Diagnostics), 6 ml blood was taken to the biochemistry tube to check for myeloperoxidase, catalase, ceruloplasmin, albumin, IMA, thiol- disulfide balance. After 5 minutes (reperfusion 1) and 20 minutes (reperfusion 2) following the lowering of the tourniquet, blood samples were taken for the same parameters. After blood samples were taken, tramadol 100 mg iv was administered in at least 60 seconds for postoperative analgesia in both groups. In the post-op period, 3 × 100 mg iv tramadol and when necessary meperidine 50 mg intramuscularly were ordered as clinical standard. No additional analgesic difference was observed in both groups. 8 and 16 hours after the first dose of ibuprofen, the vial containing 400 mg/4ml of ibuprofen IV solution for infusion was diluted intravenously in 30 minutes with a solution of 250 ml 0.9% NaCl. Group K was infused intravenously in 30 minutes with a 250 ml 0.9% NaCl solution. At postoperative 24th-hour, 6 ml blood samples were taken from both groups to evaluate TOS (total oxidant status), TAS (total antioxidant status), paraoxonase, myeloperoxidase, catalase, ceruloplasmin, and thiol balance. Fasting blood samples were taken from the volunteers into flat tubes. Serum was separated after centrifugation at 1600 g for 10 minutes and maintained at −80˚C until analysis time. Catalase (CAT) activity was measured by Goth's method (57). The sample (2 ml) was incubated for 60 seconds at 37 degrees in 1 ml of the substrate (60 mmol/L sodium-potassium phosphate buffer for 65 μmol H_2O_2 pH 7.4). The enzymatic reaction was stopped with 1.0 ml of 32.4 mM ammonium molybdate and the yellow complex of molybdate and H_2O_2 was measured against blinded at 405 nm. A CAT unit was decomposed under these conditions to 1 μmol H_2O_2 min^{-1}. The results are expressed in kU/L calculated as follows. Serum catalase activity (KU/l) = (A (blind 2) − A (blind 3)/A (sample) − A (sample 1)) × 271 Blind 1 contained 1.0 ml substrate, 1.0 ml molybdate and 0.2 ml sample. Blind 2 contained 1.0 ml of the substrate, 1.0 ml of molybdate and 0.2 ml of buffer. Blind 3 contained 1.0 ml buffer, 1.0 ml molybdate and 0.2 ml buffer.

Serum Myeloperoxidase (MPO) activity was measured by a modification of the o-dianisidine method based on the kinetic measurement at 460 nm with the rate of yellowish-orange product formation from the oxidation of o-Dianisidine with MPO in the presence of hydrogen peroxide (H_2O_2). One unit of MPO was defined as reducing 1 μmol H_2O_2 min^{-1} at 25˚C. The molar extinction coefficient of 1.13 × 10 4 oxide o-dianisidine was used for the calculation. MPO activity expressed in units of serum per liter [5]. CLP levels were measured by the method

described by Erel O. (1998). The method is automatic, colorimetric and based on enzymatic oxidation of ferrous ion to ferric ion. Results are expressed in units of serum per liter [6].

Paraoxonase and arylesterase activities were measured using commercially available kits. (Relassay, Gaziantep, Türkiye). Paraoxonase activities were measured in the absence and presence of NaCl (basal activity) (Paraoxonase induced by salt-induced activity (SPON)).

The paraoxon hydrolysis rate (diethyl-p-nitrophenyl phosphate) was measured by monitoring the absorbance increase at 412 nm at 37˚C. The amount of p-nitrophenol formed was calculated from the absorbency coefficient of 18,290 M^{-1} cm^{-1} at pH 8.5. [7]. Paraoxonase activity was expressed as U/L serum. Phenylacetate was used as a substrate to measure arylesterase activity. Enzymatic activity was calculated from the molar absorption coefficient of the produced phenol using 1310 M^{-1} cm^{-1}. One unit of arylesterase activity was defined as 1 umol phenol per minute produced under the above conditions and expressed as KU/L serum [8]. TOS was measured using a new automated colorimetric method described by Erel (2005). In this method, the oxidants present in the sample oxidize the ferrous ion-dianisidine complex to the ferric ion. The oxidation reaction is increased with glycerol molecules which are abundant in the reaction medium. The iron ion (ferric ion) forms a colored complex with xylenol orange in an acidic environment. The color intensity that can be measured spectrophotometrically relates to the total amount of oxidant molecules present in the sample. The test was calibrated with hydrogen peroxide and the results expressed in micromolar equivalents of hydrogen peroxide per liter (μmol H_2O_2 Eqv./L) [9]. TAS was measured with a new automatic colorimetric measurement method developed by Erel. In this method, the dark blue-green colored 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical of the antioxidants in the sample is reduced to the colorless ABTS radical. The absorbance change at 660 nm is related to the total antioxidant level of the sample. This method determines the antioxidant effect of the sample against strong free radical reactions initiated by the generated hydroxyl radical. The results are expressed as millimolar trolox equivalent per liter [10]. For the determination of ischemia-modified albumin (IMA), the method developed by Bar-Or *et al.* was used [11]. The so-called albumin cobalt binding test (ACB) is based on the binding of serum albumin and the transition metal cobalt.

Blood thiol-disulfide parameters were studied on Roche Hitachi Cobas c501 automatic analyzer by automatic measurement method developed by Erel & Neselioglu. Dynamic disulfide bonds (–S – S–) were reduced by sodium borohydride (NaBH4) to functional thiol groups (–SH) and unused NaBH4 residues were eliminated by formaldehyde. Thus, the extra reduction of Ellman's reagent was prevented and the total thiol content of the sample was measured with modified Ellman's reagent (Classic Ellman's reagent modified by adding formaldehyde). The difference between total thiol and native thiol was divided into two

and the disulfide bond amount was obtained [12].

3. Statistical Analysis

Statistical analysis was performed using version 18 of the SPSS software. Normal distribution was evaluated using the Kolmogorov-Smirnov Test. Chi-Square Test was used to compare genders in Case and Control groups. The student's T-test was used to compare the normal distribution of the values and the mean ± standard deviation was obtained. Values with abnormal distribution were compared using either the Mann Whitney U test or Wilcoxon test and the values were given as mean (interquartile range). Correlation between test results and tourniquet time analysis was evaluated using the Pearson Test due to the normal distribution of these parameters. A p-value of < 0.05 indicates that it is statistically significant.

4. Results

62 patients were included in the study. Of these, 20.9% were male and 79.1% were female. The mean age of the case group was 65.87 ± 6.23 years, while the mean age of the control group was 64.13 ± 7.61 years. The mean BMI of the case group was 31.20 (7.60) and 31.80 (5.18) in the control group ($p = 0.905$). The tourniquet time was 85.00 (27) minutes in the case group and 84.50 (46) minutes in the control group ($p = 0.972$). There was no statistically significant difference between the two groups in terms of demographic data. Demographic data are given in Table 1.

There was no statistically significant difference between the two groups in terms of hemoglobin and mean arterial pressure (MAP) ($p > 0.05$).

When the thiol values were compared, the values of native thiol in measurements 1, 2, 3 and total thiol in measurements 1 and 2 were found to be significantly lower in the case group compared to the control group. When the basal and 24th-hour results of the case group were compared in terms of thiol values, no statistical difference was found. In the control group, disulfide, disulfide/native thiol, disulfide/total thiol values increased significantly in the 24th-hour as the tourniquet time increased and the native/total thiol levels were found to be low. In the control group, the normal thiol total thiol and native/total ratio increased significantly and the disulfide/native and disulfide/total ratio were significantly lower in the 24th-hour comparison with basal.

Table 1. Demographic data.

	Case Group	Control Group
Gender (M/F)	6/25	7/24
Age (Year)	65.87 ± 6.23	64.13 ± 7.61
BMI (kg/m²)	31.20 (7.60)	84.50 (46)

Albumin baseline values ($p = 0.440$) and post-op at 24th-hour ($p = 0.226$) were not statistically significant between the two groups, while 1) (ischemia period, $p = 0.005$); 2) (5th minute of reperfusion, $p < 0.001$); 3) (20th minute of reperfusion, $p < 0.001$) values were significantly lower in the case group.

IMA (Ischemia Modified Albumin) basal ($p = 0.795$), 1st (0.169) and 24-hour post-op ($p = 0.169$) values were not statistically significant different, while 2nd (0.062) and 3. ($p = 0.045$) values were significantly higher in the case group.

There was no statistically significant difference in TAS (Total Antioxidant Status) basal ($p = 0.436$), 1. ($p = 0.332$), 2. ($p = 0.979$), and 3. ($p = 0.490$) values and post-op was significantly lower in the case group at 24 hours ($p = 0.030$).

Ferroxidase basal ($p = 0.18$) 1. ($p = 0.266$), 2. ($p = 0.509$), 3. ($p = 0.643$), post-op at 24 hours ($p = 0.111$) values were not significantly different.

PON (Paraoxenase) basal 1st ($p = 0.130$), 2nd (0.077), post-op 24th-hours ($p = 0.074$), there was no statistically significant difference between the values and 3. ($p = 0.032$) value was significantly lower in the case group. There was no statistically significant difference between the two groups in TOS measurements. There was no statistically significant difference between the groups in terms of arylesterase measurements ($p > 0.05$). There was no statistically significant difference between the two groups in catalase measurements ($p > 0.05$). There was no statistically significant difference between the two groups in myeloperoxidase measurements ($p > 0.05$). Comparison of basal and 24th-hour results in the patient group ($n = 31$); Compared to basal values, we observed that there was a statistically significant decrease in TAS, PON, ferroxidase, arylesterase, and albumin values at 24 hours postoperatively, whereas IMA values were significantly increased.

Comparison of basal (n: 31) and 24th-hour results in the control group; There was a statistically significant (p: < 0.001) decrease in TAS, PON, ferroxidase, arylesterase, and albumin values, whereas IMA values were significantly increased.

5. Discussion

Ischemia-reperfusion injury (IRI) has been the subject of many studies [1] [13]. The common goal of these studies is to identify the factors and the agents that may reduce IRI damage; thus minimizing the damage caused by IRI damage to the organism. Total knee arthroplasty is an elective surgical procedure that is commonly performed today and many surgeons use pneumatic tourniquets to provide a clean surgical site and reduce bleeding [1]. Ibuprofen is a drug known for its analgesic, antipyretic, anti-inflammatory effects [3]. Haagen *et al.* (2017) studied the effect of single-dose preemptive IV ibuprofen on opioid consumption and postoperative pain in the first 24 hours in patients with laparoscopic cholecystectomy and showed that single-dose IV ibuprofen reduced opioid use by 45% in this patient group [14]. Many pain studies with IV ibuprofen have shown that ibuprofen reduces opioid use, reduces the rate of nausea and vomit-

ing, causes a significant decrease in the Visual Analogue Scale (VAS) on the move and at rest, significantly shortening the ambulation time of patients [15] [16]. In the study performed by Sivgin *et al.*, the effect of IV ibuprofen and lornoxicam on erythrocyte deformity in hind limb ischemia-reperfusion injury in rats was investigated. And both drugs did not cause erythrocyte deformity [17]. In our study, we hypothesized that the anti-inflammatory mechanism of intravenous ibuprofen might play a role in reducing oxidative stress and reduce ischemia-reperfusion injury caused by the tourniquet.

Thiol groups are important molecules that protect the organism from harmful effects and reactive oxygen species. Thiol disulfide equilibrium is a simple and novel method of measuring oxidative stress. In a study by Dr. Gul *et al.* (2018), which examined thiol-disulfide homeostasis in varicocele infertile men, disulfide concentration, disulfide/native thiol, disulfide/total thiol ratios were found to be high in patients with infertile varicocele. It was concluded that thiol-disulfide ratios can be used as an oxidative stress marker in this group of patients [18]. In another study conducted in 2018; total thiol, native thiol, disulfide levels were measured in 40 pediatric patients with febrile convulsion (FK) history and 40 healthy children within a similar mean age and sex distribution and thiol homeostasis was evaluated. Thiol disulfide, disulfid/native thiol, disulfid/total thiol levels were significantly higher in the group with FK history. As a result; higher thiol-disulfide in the FK group and lower native thiol in the FK group suggest that oxidants alter the thiol balance and play an important role in the pathogenesis of FK [19]. Köseoğlu H. *et al.* evaluated the thiol-disulfide homeostasis in patients with acute pancreatitis and found the disulfide/total thiol, disulfid/native thiol ratio higher in the acute pancreatitis group compared to the control group [20]. Many studies in recent years support that thiols are the most important antioxidant agents and thiol-disulfide homeostasis is a new oxidative stress marker [18] [19] [21]. In our study, when the two groups were compared, it was found that the native thiol and total thiol values were significantly lower in the patient group compared to the control group. Native thiol and total thiol levels were found to be low in the 24th-hour blood compared to basal blood of the patient group and no statistically significant difference was found in thiol-disulfide, disulfide/native thiol, disulfide/total thiol levels. Compared to basal values in the control group, the values of native thiol, total thiol, and native/total thiol were significantly increased in the 24th-hour; disulfid/native thiol and disulfid/total thiol levels were significantly lower. This change in the control group may show us that the oxidative balance in patients after total knee replacement surgery shifts towards antioxidants. In this case, it can be concluded that IV ibuprofen acts on thiol balance in favor of oxidants.

TAS measurement is a measure of the protective effect of plasma antioxidants, and also shows the rate of consumption of antioxidant production due to oxidative stress [22]. In a study published by Khazan *et al.* In 2018, the level of oxidative stress biomarkers in patients with herpes zoster compared to the control

group was investigated. TAS, TOS, oxidative stress index (OSI), glutathione (GSH), superoxide dismutase and total phenol content (TPC) levels were studied. In herpes zoster group, TAS and TPC were found to be very low, however, TOS and OSI were found to be high. A significant negative correlation was found between TAS and TPC and TOS. Oxidative stress imbalance was interpreted as present in this group of patients [23]. In our study, TAS values were significantly lower in both case and control groups at the post-op 24th-hour, and when the two groups were compared, the statistically significant lower values of the case group in the 4th blood samples may indicate that ibuprofen had a negative effect on total antioxidant status.

TOS shows the overall assessment of the total oxidant molecules in the organism [9]. In a study published in 2018, the effects of melatonin and glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide on the gastric ischemia-reperfusion injury was evaluated in rats fed high fat and sucrose diet. The rats were divided into three groups: TAS, TOS, OSI, BMI were calculated and histopathological examination was performed. TOS, OSI, and BMI were high and TAS was low in the fat-rich diet. This effect was reversed in the other two groups given melatonin and liraglutide. The effect of two drugs in preventing oxidative stress is shown on these parameters [24]. In our study, the fact that TOS was not statistically significant in both groups may indicate that ibuprofen does not contribute to TOS value. Paraoxonase gene family has 3 members: PON 1, PON 2, PON 3. The most studied group was PON 1; plasma, an antioxidant enzyme bound to high-density lipoprotein (HDL) and protects low-density lipoprotein (LDL) and HDL against oxidation [25]. Paraoxonase is synthesized in the liver, hydrolyzes phospholipid hydroperoxides and cholesterol ester hydroperoxides [26]. In a study on paraoxonase activity in metabolic syndrome (MS) in adolescents and children; Serum PON, ARE, lactonase (LACT) activity were measured in MS and control groups. The activity of all these antioxidant enzymes was low in children with MS. There was a significant correlation between PON1 activity and BMI. Low PON1 activity in children and adolescents with MS would be due to abnormalities in HDL cholesterol synthesis and secretion, as well as oxidative stress in the overproduction of free radicals [27]. PON was significantly lower in both case and control groups at 24th-hour compared to basal and was found to be lower in the case group in the 3rd blood compared to the two groups. It is also the only value correlated with tourniquet time. In a study conducted by Dilek *et al.* in 2016, low levels of ibuprofen, larmeloxicam, and methotrexate which are commonly used in patients with rheumatoid arthritis inhibit paraoxonase enzyme activity by different mechanisms [28]. In our study, the decrease in PON level in both groups may be related to the longer tourniquet time, and the lower blood level of the case group in the 3rd blood compared to the control group may be due to ibuprofen inhibiting enzyme activity or reducing antioxidants such as the effect on TAS and thiol balance. Paraoxonase 1 and arylesterase are enzymes encoded by the same gene and have similar active centers. When we

look at the arylesterase values, we can see that there is no significant difference between the two groups and there is a significant decrease in both groups at the 24th-hour.

Ibuprofen does not appear to affect arylesterase.

Human serum albumin (HSA) is the most abundant plasma protein in the circulation. In addition to its significant contribution to oncotic pressure, it regulates many physiological processes such as the balance of redox status, the inflammatory and/or immunological response, and the pharmacokinetics and pharmacodynamics of many drugs, and undergoes structural and functional changes in systemic inflammation and oxidative stress [29]. Furthermore, the fact that HSA has several ligand binding and transport sites, including ibuprofen, has been shown in a study by Evoli S. *et al.* (2016) [30]. Albumin was significantly lower in the case and control group at 24th-hour compared to the basal value. In the reperfusion period of the case group (2nd and 3rd blood) it was lower than the control group. It is thought that the cause of albumin fall in both groups is IRI due to tourniquet. The reason that in the case group it is lower during the reperfusion period can be interpreted as the binding of ibuprofen to albumin or it may be due to the decrease in antioxidants of ibuprofen.

D. Sauza J. *et al.* (2017) compared hypertension patients with increased protein oxidation products, ischemia-modified albumin (IMA) with TAS and total thiol in a study performed in hypertensive patients other than arthroplasty during pregnancy. As a result, a significant increase in increased oxidized protein products and IMA levels; TAS and total thiol decreased significantly [31]. This study supports the hypothesis that protein oxidation with increased oxidative stress, decreased antioxidant status, and negative correlation between protein oxidation and TAS in these patients. In a study of 30 patients who underwent coronary artery bypass surgery, IMA levels were measured in preop, intraop and postop periods. Postoperative hemodynamic parameters (AF, ventricular arrhythmias) were evaluated. Intraoperative IMA values were significantly higher than the preoperative and postoperative periods. AF ratio and inotropic requirements were found to be parallel with the IMA level. It is concluded that IMA is one of the early rising markers in the case of cardiac ischemia [32]. In our study, a significant increase in IMA in both groups compared to basal values at post-op 24th-hour may mean that ibuprofen did not affect the IMA level, but a significant decrease in reperfusion in the case group at the 20th minute could be interpreted as ibuprofen is lowering the IMA level. The 20th minute of reperfusion corresponds to about 110 minutes after ibuprofen (800 mg) infusion. We think that if the doses we used after the first dose (400 mg × 2) were higher, it could affect the IMA level at the 24th-hour. Further studies using higher doses of medication may be needed.

Ceruloplasmin, a copper-containing enzyme with ferroxidase activity, is necessary for iron to enter the hemoglobin structure since it provides oxidation of divalent iron to trivalent iron before it binds to transferrin. Cytochrome oxidase containing copper is the terminal oxidase in the respiratory chain and catalyzes

the reduction of oxygen to water. The fact that ferroxidase decreased at 24th-hour compared to the basal value in both groups may be attributed to IRI and no difference between the two groups indicates that ibuprofen does not affect this parameter at the doses used. Catalase is an antioxidant that removes hydrogen peroxide. Myeloperoxidase (MPO) is an enzyme in the granules of mammalian neutrophils and plays an important role in the killing of phagocytosed bacteria. There was no significant decrease or increase in catalase and myeloperoxidase levels in both groups. It can be concluded that intravenous ibuprofen does not affect these enzymes at the doses used.

6. Conclusion

We observed that antioxidants decreased and oxidants increased on the first postoperative day in both groups in patients. The decrease in antioxidant parameters was higher in IV ibuprofen doses compared to the control group in the case group; these doses indicate that the drug adversely affects the organism in the fight against oxidative stress, which is an undesirable effect. To evaluate this negative effect of IV ibuprofen which is increasingly used in postoperative analgesia, studies with different doses of drugs and different surgeries may be needed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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